Compound	λ_{max}^{alk}	λ_{max}^{acid}
Cevagenine D-orthoacetate[20]	316 mμ (ε, 3000)	274 (ε, 5000)
Cevagenine C-orthoacetate[20]	316 mμ (ε, 3000)	275 (ε, 5000)
Isogermine[18]	320 mμ (ε, 3000)	275 (ε, 3800)
Cholestane-3β,7α-diol-4-one[28]	320 mμ (ε, 6300)	278 (ε, 8100)

Color Reactions of Sabadine (VII) and Sabine Orthoacetate (XIX) with Potassium Tetramethyl Osmate and Potassium Triacetyl Osmate.[29]—Sabadine (2 mg.) was added to a solution of potassium tetramethyl osmate (2 mg.) in methanol (0.5 ml.). The blue color of the osmate solution was changed immediately to yellow-green and then to brown. Treatment of sabine orthoacetate (2 mg.) in the same manner caused no change in the color of the osmate solution for 2 days.

Sabadine (2 mg.) was added to the cobalt-blue solution prepared by dissolution of potassium tetramethyl osmate (2 mg.) in glacial acetic acid (0.5 ml.). The solution changed in color immediately to a dark red-violet which was unchanged after addition of potassium acetate (10 mg.). Treatment of sabine orthoacetate (2 mg.) in the same manner led to a gradual change in color of the solution to a dark red-violet. Addition of potassium acetate (10 mg.) caused the color to change back to deep blue.

Degradation of Corticosteroids. VII. The Synthesis of 7-Membered Ring-A Enol-Lactones[1]

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Treatment of Δ^4-3-keto steroids with perbenzoic acid in the presence of perchloric acid gave 3-oxo-3a-oxa-enol lactones. The antiestrogenic activity of several lactones was evaluated.

Steroidal enol lactones of the type (II) were required for studies concerning the degradation of corticosteroids.[3–5] The Baeyer–Villiger oxidation[6,7] is frequently employed for the conversion of ali-

(1) This work was supported by grants from the American Cancer Society, Inc., P-102 and P-103.

(2) Post-doctoral fellow 1956–1957.

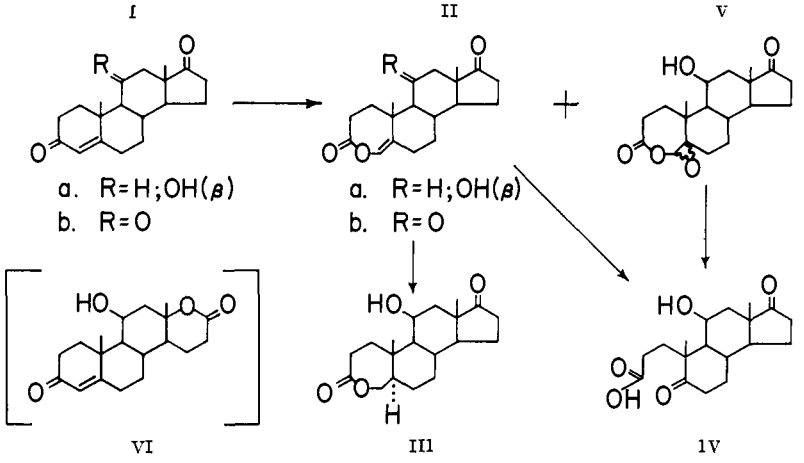
(3) E. Caspi, Symposium on the Biosynthesis of Lipids, Vth Internat. Congress of Biochemistry, Moscow, August 10–16, 1961, Vol. VII, Preprint 80.

(4) E. Caspi, 140th Meeting, American Chemical Society, Chicago, Ill., Sept. 5, 1961. Abstract p. 29-Q.

(5) E. Caspi, R. I. Dorfman, B. T. Khan, G. Rosenfeld, and W. Schmid, *J. Biol. Chem.*, in press (1962).

(6) A. Baeyer and V. Villiger, *Ber.*, **32**, 3625 (1899).

(7) C. H. Hassall, *Org. Reactions*, **9**, 73 (1957).



cyclic ketones to lactones. Evidence was provided that the nature of the lactones formed depends on steric as well as electronic factors.[7,8] In the case of α,β-unsaturated cyclic ketones the reaction is more complex, because of the availability of several routes of attack.[9] The presence in the molecule of other groups, *e.g.*, keto groups, which might compete for the oxidizing species constitutes further complications.[10,11] The catalytic influence of acids on the rate of the Baeyer–Villiger oxidation was conclusively demonstrated.[11] We have anticipated that a strong acid catalyst, *i.e.*, perchloric acid, may decrease the side reactions and improve the yield of the desired product. The reaction of perbenzoic acid with Δ^4-3-keto steroids in the presence of perchloric acid was investigated and is herein described. The antiestrogenic activity of some enol lactones is reported.

A solution of 11β-hydroxyandrost-4-ene-3,17-dione (Ia) in chloroform saturated with perchloric acid was treated with 1.2 equivalents of perbenzoic acid, and the mixture was allowed to react for 16 hours at room temperature. At the termination of the reaction all the active oxygen was utilized. Processing of the reaction mixture gave a neutral product (IIa) (49% yield) which was devoid of selective ultraviolet light absorption in the 220–240 mμ region but showed pronounced end absorption. This indicated that the perbenzoic acid attacked the conjugated ketone in ring A. The substance analyzed as $C_{19}H_{26}O_4$, and exhibited infrared absorption at 3400, 1740, 1735 and 1640 cm^{-1}. The possibility of the product being the 3-keto-4,5-epoxide

(8) J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, **82**, 5235 (1960), and references.
(9) Reference 7, p. 81.
(10) L. H. Sarett, *J. Am. Chem. Soc.*, **69**, 2899 (1947).
(11) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1768 (1949).

was excluded because of the strong end absorption in the ultraviolet, and the relatively intense band at 1640 cm.$^{-1}$ in the infrared, which when taken together with the carbonyl absorption is indicative of an enol lactone.[12,13] It was evident that a Baeyer–Villiger reaction had taken place, and that (IIa) must be an enol lactone. The presence of the double bond was confirmed by hydrogenation of (IIa) to the saturated seven-membered lactone (III). The saturated lactone (III) was tentatively assigned the 5α-configuration on the assumption that the addition of hydrogen proceeded from the more accessible α-side of the molecule. Conclusive evidence for the enol lactone structure was provided by ozonolysis of (IIa) to the previously described[13,14] 4-norketo acid (IV). Oxidation of (IIa) with chromium trioxide in pyridine gave the 11-keto-enol-lactone (IIb), which was alternatively prepared from adrenosterone (Ib) by treatment with perbenzoic acid as described for (Ia). Chromatographic fractionation of the mother liquor of (IIa) gave an additional amount of the lactone (IIa). The over-all yield of the enol lactone isolated was about 60%.

From the chromatography column two more products were eluted. The major substance (V) was obtained in 8% yield and analyzed for $C_{19}H_{26}O_5$. The substance neither absorbed ultraviolet light selectively in the 220–240 mμ region nor did it show end absorption. Its infrared spectrum had bands at 3550, 1730, 1260 and 1190 cm.$^{-1}$. Attempts to hydrogenate the product in absolute ethanol using 5% palladium on charcoal as catalyst failed, and no uptake of hydrogen was observed. Structures of 4-epoxy-3-keto-13,17-lactone, and 4-epoxy-3,4-lactone were considered for the unknown, because both could account for the absence of unsaturation, and for the incorporation of two oxygen atoms in the molecule. The epoxy lactone structure (V) was proven for the product by its conversion in two steps to the acid (IV). The epoxide was first treated with aqueous methanolic sulfuric acid, and then the formed product was cleaved *in situ* with periodic acid to yield (IV). Although (V) was probably the 4α,5α-epoxide formed by the attack from the back side of the molecule, no attempts to assign the configurations were made.

In addition, a small amount of another substance, which probably was the Δ^4-3-keto-13,17-lactone (VI), was eluted from the column. Unfortunately, lack of material prevented its identification.

In the two cases investigated, the major products formed were the

(12) H. Rosenkrantz and M. Gut, *Helv. Chim. Acta*, **36**, 1000 (1953); T. L. Jacobs and N. Takahashi, *J. Am. Chem. Soc.*, **80**, 4865 (1958).

(13) E. Caspi, B. T. Khan, and W. Schmid, *J. Org. Chem.*, **26**, 3894 (1961).

(14) E. Caspi, W. Schmid, and B. T. Khan, *ibid.*, **26**, 3898 (1961).

3,4-enol lactones which arose *via* the Baeyer–Villiger reaction. It can be concluded that the attack of the oxidizing species was directed at least mainly toward the conjugated ketone in ring A. In the case of 11β-hydroxyandrost-4-ene-3,17-dione (Ia), the reaction residue was carefully fractionated and no appreciable amounts of products arising from the attack on the C-17 carbonyl were found. The 4-epoxy lactone (V) was likely the result of further attack of the peracid on the enol lactone (IIa).

Pettit and Kasturi[15] have recently investigated the oxidation of α,β-unsaturated ketones to saturated lactones with persulfuric acid, and have suggested the intermediate formation of enol lactones. This suggestion finds experimental support in our results. It might be inferred from the observations reported that the enol-lactones are intermediates not only of the persulfuric acid oxidation but of all peracid oxidations of conjugated ketones in the presence of strong acidic catalysts. Whether the catalyst has a controlling influence on the course of the reaction is not clear from the present data and is being investigated.

Three compounds were studied as possible antiestrogens in a test involving the uterus of the estrone stimulated immature mouse.[16] The results, consisting of three separate experiments, are reported in Table I and indicate that compounds IIb and V at the 1 mg. dose levels were inactive. Compound IIa was inactive at the 1 mg. dose level but produced a statistically significant reduction in estrone stimulation of the uterus on one occasion at the 2 mg. dose level (Experiment II) and twice at the 4 mg. dose level (Experiments II and III). Compound IIa is of particular interest since it is antiestrogenic and not androgenic on the chick's comb even at 100 times the minimal dose of testosterone.

Experimental[17]

Treatment of 11β-Hydroxyandrost-4-ene-3,17-dione (Ia) with Perbenzoic Acid.—Chloroform was agitated with an aqueous 70% solution of perchloric acid, then the phases were separated. The 11β-hydroxyandrost-4-ene-3,17-dione (Ia) (6.58 g.) was dissolved in the prepared chloroform (45 ml.) and a solution of perbenzoic acid in chloroform (42.7 ml.) containing 70 mg. of perbenzoic acid per ml. was added to the mixture. Samples were removed at intervals and assayed

(15) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961).

(16) R. I. Dorfman, F. A. Kincl, and H. J. Ringold, *Endocrinology*, **68**, 17 (1960).

(17) Melting points were determined on a micro hot stage and are corrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratories, New York. Ultraviolet absorption spectra were determined by means of a Cary 11MS spectrophotometer on methanolic solutions. Infrared spectra were determined on solids incorporated in potassium bromide disks.

TABLE I

ANTI-ESTROGENIC ACTION OF COMPOUNDS IIA, IIB, AND V BY SUBCUTANEOUS INJECTION

Exp. no.	Test compound (total dose mg.)	Total dose of estrone, μg.	No. of mice	Mean uterine ratio ± S.E.
I	0	0	10	0.91 ± 0.047
	0	0.32	14	5.03 ± 0.245
	IIb (1.0)	0.32	10	4.93 ± 0.227
	V (1.0)	0.32	9	4.74 ± 0.273
II	0	0	10	1.00 ± 0.192
	0	0.4	10	5.41 ± 0.242
	Deoxycorticosterone (2.0)	0.4	10	3.81 ± 0.230
	IIa (0.1)	0.4	9	5.42 ± 0.149
	IIa (0.5)	0.4	10	5.62 ± 0.234
	IIa (1.0)	0.4	9	5.29 ± 0.070
	IIa (2.0)	0.4	9	4.82 ± 0.137
	IIa (4.0)	0.4	10	4.66 ± 0.331
III	0	0	10	1.10 ± 0.076
	0	0.4	9	5.54 ± 0.195
	Deoxycorticosterone (1.0)	0.4	9	4.98 ± 0.411
	IIa (4.0)	0.4	9	3.08 ± 0.224

for active oxygen.[18] After 16 hr. at room temperature the active oxygen was consumed. The solution was then thoroughly washed with a sodium hydrogen carbonate solution, water, then dried, and concentrated to yield 7.1 g. of a crude residue. Crystallization of the residue from methanol gave (IIa) (3.38 g.), m.p. 214–222°. The residue from the mother liquor was chromatographed on silica gel to yield (IIa) (750 mg.), some starting material (Ia), then (V) (610 mg.) and finally a small amount of a product which was probably (VI), λ_{max}^{MeOH} 240 mμ, ν_{max}^{KBr} 3500, 1740, 1675, 1620 cm.$^{-1}$.

A-Homo-3a-oxa-11β-hydroxyandrost-4-ene-3,17-dione (IIa).—Several recrystallizations from methanol gave crystals, m.p. 224–226°, λ_{max}^{MeOH} no specific absorption in the 220–240 mμ region except for end absorption, ν_{max}^{KBr} 3400, 1740, 1735, and 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.86, 72.15; H, 8.33, 8.10.

A-Homo-3a-oxa-11β-hydroxy-5α-androstane-3,17-dione (III).—To a solution of (IIa), 56.2 mg., in absolute ethanol, 5% palladium on charcoal catalyst (20 mg.) was added, and the mixture was agitated in an atmosphere of hydrogen at 23.5° (746.7 mm.) After 25 min. the uptake of hydrogen was 4.01 ml. The catalyst was collected by filtration, and the filtrate was concentrated to yield (III). The product crystallized from methanol, m.p. 275–276°, λ_{max}^{MeOH} no specific absorption in the 220–240 mμ region and very little end absorption, ν_{max}^{KBr} 3500, 1730, 1725, 1290, 1190 and 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.42; H, 8.95.

(18) A. I. Vogel, in "Practical Organic Chemistry," Longman, Green & Co., London, 3rd Edition, 1956, p. 809.

3,5-Seco-4-nor-11β-hydroxyandrostane-5,17-dione-3-oic acid (IV).—(a) A solution of (IIa) (119 mg.) in methylene chloride (14 ml.) was treated at −70° with a stream of ozonized oxygen. Aqueous 30% hydrogen peroxide (2 ml.) was added, and the mixture was agitated for 16 hr. at room temperature. The aqueous phase was discarded, and the acid (IV) (57.6 mg.), m.p. 201–202°, was recovered in the conventional manner *via* partition with base. The infrared spectrum of (IV) was identical to that of an authentic sample.

(b) A mixture of (V) (26 mg.), methanol (3 ml.) and 2 *N* sulfuric acid (0.3 ml.) was stored for 16 hr. at room temperature. Then, periodic acid dihydrate (30 mg.), dissolved in a small amount of water, was added and the solution was allowed to stand at room temperature for 24 hr. Water was added, and (IV) was recovered in the usual manner.

A-Homo-3a-oxa-4ξ,5ξ-epoxy-11β-hydroxyandrostane-3,17-dione (V).—A sample of the epoxy lactone (V) was crystallized from methanol; m.p. 250–251°; λ_{max}^{MeOH} no specific absorption in the 220–240 mμ region; ν_{max}^{KBr} 3550, 1730, 1260, 1190 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.33, 68.48; H, 7.76, 7.98.

When a solution of (V) (40.9 mg.) in absolute ethanol (5 ml.) was agitated for 3 hr. with 5% palladium on charcoal (20 mg.) in an atmosphere of hydrogen, no uptake of gas was observed.

A-Homo-3a-oxa-androst-4-ene-3,11,17-trione (IIb).—(a) To a solution of adrenosterone (1 g.) in chloroform saturated with perchloric acid (16 ml.) a solution of perbenzoic acid in chloroform (8 ml.; 70 mg. of perbenzoic acid/ml.) was added, and the mixture was stored for 16 hr. at room temperature. At the termination of the reaction all the perbenzoic acid was consumed. The mixture was processed as described for (IIa) to yield a glass (1.13 g.) which upon trituration with ethyl acetate gave unchanged adrenosterone (106 mg.). The mother liquor was chromatographed on a silica gel column prepared with benzene-ethyl acetate (19:1). The enol lactone (IIb) (270 mg.) was eluted with a mixture of benzene–ethyl acetate (2:1).

(b) A solution of (IIa) (50 mg.) in pyridine (1.0 ml.) was added to a suspension of chromium trioxide (50 mg.) in pyridine (0.5 ml.) and the mixture was allowed to react for 16 hr. at room temperature. The product (IIb) was recovered as previously described.[14] Both samples gave identical infrared spectra and showed a m.p. 247–249°; ν_{max}^{KBr} 1737, 1700 and 1650 cm.$^{-1}$.